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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,732	08/25/2003	Thomas T. Chen	97511.00005	2152

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EXAMINER
O'HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/647,732	CHEN ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-10 and 16-23* is/are pending in the application.

4a) Of the above claim(s) *6-10 and 16-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *6-10 and 16-23* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 December 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 6-10 and 16-23 are pending in the instant application.

Election/Restrictions

2. Applicant's election with traverse of Group II in the reply filed on July 7, 2006 is acknowledged. The traversal is on the ground(s) that Applicant believes that Group I and Group II do not represent independent or distinct inventions. Applicants assert that the inventions as claimed are in the same class and are related by design, operation and effect. Applicants argue that it is illusory to refer to the nucleic acid and the protein it encodes as separate and distinct inventions due to the unique physical and chemical relationship that exists between the two, and because of the close relationship that exists between the two, it is very unlikely that the literature or the patent art would make reference to one with no reference whatsoever to the other, and therefore the search and examination of the claims of Group I can be made without serious burden to the Examiner. This is not found persuasive because consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search:. These criteria were met in the above restriction. The subclasses of the groups differ. Also, a separate field of search would be required, since examination of the gene therapy claims would require not just a search of the sequences but a search of the state of the art of gene therapy for enablement purposes. Therefore, separate searches would be required for the two groups. As stated in the MPEP § 803, "a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02.". Thus, the groups require

divergent searches and consideration, and to search and consider all inventions would be burdensome.

The requirement is still deemed proper and is therefore made FINAL.

It is noted that claims 16-20 are drawn to administering a nucleic acid encoding an E-domain peptide agent, which is the subject matter of Group I, and these claims were mistakenly placed in Group II, drawn to administering an E-domain peptide agent. Therefore claims 16-20 are in GroupI.

Claims 6-10 and 16-20 are withdrawn as being drawn to a non-elected invention.

Claims 21-23 are currently under examination.

Priority

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). There is no reference to this application being a continuation of application 09/669,642, filed September 26, 2000, now United States Patent No. 6,610,302. Additionally, This application lacks the current status of the nonprovisional parent application 09/120,818. A statement reading "(now United States Patent No. 6,358,916)" should be included after "09/120,818, filed July 22, 1998" following the title of the invention or as the first sentence of the specification.

Specification

4.1 The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: claims are directed to E-domain peptide agents, trout-E-domain peptide, E-domain peptide homologs and E-domain peptide fusions, and there are no definitions of these embodiments in the specification. Although the specification of the parent case 09/120,818 was incorporated in its entirety into the instant application, and these embodiments are defined on pages 4-6 of the parent case, the definitions need to be added into the instant specification.

The disclosure is objected to because of the following informalities:

4.2 On the first page of the specification under Field of the Invention, the typographical error "pro-**IFG**-I" is written twice, and should be corrected to "pro-**IGF**-I".

4.3 On page 1, 3rd line after Brief Description of the Related Art, the word "biological" should be "biologically".

4.4 On page 12, Example 3, second line of Overview, the phrase "three of the **know Ea-4-peptides**" should be "three of the **known Ea-peptides**".

4.5 On page 13, Example 4, second line of Overview, the word "lost" should be "loss".

Appropriate correction is required.

Drawings

5. The set of Formal Drawings filed December 11, 2003 are missing Fig. 7., which is referred to on pages 8 and 17. It is recommended that a complete set of drawings be submitted in order to ensure printing of all the figures.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6.1 Claims 21-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28-71 (renumbered as 1-44) of copending Application No. 10/100,492. Although the conflicting claims are not identical, they are not patentably distinct from each other because they both encompass a method of inhibiting proliferation or reducing the invasiveness of malignant cells comprising administration of Ea-2 or Ea-4 domain peptides, wherein they may or may not be fusion proteins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6.2 Claims 21-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of copending Application No.

11/354,484. Although the conflicting claims are not identical, they are not patentably distinct from each other because they both encompass a method of inhibiting proliferation or reducing the invasiveness of malignant cells comprising administration of Ea-4 domain peptides (SEQ ID NO: 4 of present application is the same as SEQ ID NO: 2 of 11/354,484), wherein they may or may not be fusion proteins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6.3 Claims 21-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,610,302. Although the conflicting claims are not identical, they are not patentably distinct from each other because they both encompass a method of inhibiting proliferation or reducing the invasiveness of malignant cells comprising administration of Ea-2 or Ea-4 domain peptides, wherein they may or may not be fusion proteins.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7.1 Claim 23 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting proliferation and reducing the invasiveness of malignant cells in vitro, does not reasonably provide enablement for these methods in vivo. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 23 encompasses pharmaceutical compositions comprising isolated Ea-2 domain peptide and Ea-4 domain peptide. Thus the claim encompasses a "pharmaceutical use" for the compositions. For the claim to be enabled, the specification must teach how to use the composition for at least one pharmaceutical use without undue experimentation. Steadman's Medical Dictionary (27th Edition, online) defines "drug" as "Therapeutic agent; any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease." Ansel et al (Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Edition), says "A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in humans or in other animals. One of the most astounding qualities of drugs is the diversity of their actions and effects on the body." The following are examples of "pharmaceutical uses": administering vitamin supplements (preventing disease); using labeled antibodies for in vivo imaging (diagnosing disease); administering a substance to alleviate a symptom of a disease (alleviating or treating disease); and administering an antibiotic (curing bacterial infection).

In the present situation, to enable a pharmaceutical use for the Ea-2 domain peptide and Ea-4 domain peptide requires the specification to teach how to use the peptides, without undue experimentation, for the methods of inhibiting proliferation and reducing the invasiveness of malignant cells in the animal to which the substance is administered. However, the specification does not provide support for a method of administering the peptides in vivo. The examples in the specification are methods of treating oncogenic transformed/established tumor cell lines in

cell culture. In example 6 (pages 15-16) (Figure 6), ZR75-1 tumor cells were treated with Ea-4-peptide, and then injected into nude mice. In this example the tumors that developed were half the size of tumors from control cells. There are no working examples of administration of the peptide to an animal with an established tumor. It is not predictable from the in vitro experiments of the instant specification or from the teachings of the prior art that the Ea-2 domain peptide and Ea-4 domain peptide could be used to inhibit proliferation and reduce the invasiveness of malignant cells already established in the animal. There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

It is acknowledged that the level of skill in the art is high. However, due to the lack of direction or guidance in the specification, the absence of working examples and teachings of the prior art, the unpredictability in the art, and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use a "pharmaceutical composition" comprising Ea-2 domain peptide and Ea-4 domain peptide. However, the specification enables the use of "a composition" comprising the Ea-2 domain peptide and Ea-4 domain peptide and a pharmaceutically acceptable carrier.

7.2 Claims 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting proliferation and reducing the

invasiveness of malignant cells using Ea-2 domain peptide and Ea-4 domain peptides having the amino acid sequences of SEQ ID NOS: 2 and 4 respectively, or fusion proteins comprising those amino acid sequences, does not reasonably provide enablement for E-domain peptide agents, trout E-domain peptide or E-domain peptide homologs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification discloses four trout E domain peptides identified as Ea-1, Ea-2, Ea-3 and Ea-4 (SEQ ID NOS: 1, 2, 3 and 4 having amino acid lengths of 35, 47, 62 and 74, respectively), derived from insulin-like growth factor-I (IGF-I) after proteolytic cleavage of the pro-IGF-I protein. The specification discloses several experiments in which Ea-2 domain peptide and/or Ea-4 domain peptide have activities of inhibiting proliferation and reducing the invasiveness of malignant cells by in vitro treatment of several different oncogenic transformed/established tumor cell lines. Given the state of the art, it would not require undue experimentation for the skilled artisan to make and use fusion proteins comprising the Ea-2 and Ea-4 domain peptides, and these are also enabled. However, the specification does not provide enablement for these methods using any other E domain peptide, including E-domain peptide agents, trout-E-domain peptide or E-domain peptide homologs.

The instant specification does not teach the effect of Ea-1 (SEQ ID NO:1, 35 amino acids) on cells in culture, and also teaches that Ea-3 peptide does not have the activities of inhibiting proliferation and reducing the invasiveness of malignant cells (pages 12-13 of the specification) that the Ea-2 and Ea-4 peptides do, and that human IGF-I also does not have these activities. The Ea-2 and Ea-4 peptides are identical except for an additional insertion of 27

amino acids in the Ea-4 peptide. The Ea-3 peptide is identical to the Ea-4 peptide, except that it is missing a 12 amino acid insertion that is present in EA-4 and is also present in Ea-2 (page 3 of the specification. Even though the four rainbow trout peptides share the same amino and carboxy terminal sequences, given the fact that there is no data for the Ea-1 peptide (the smallest peptide of the four disclosed and that the closely related Ea-3 peptide and human IFG-I peptide do not have the claimed activities, and given the unpredictability in the art in determining if any other E-domain peptide would also have the claimed activities, a skilled artisan could not determine if any other E-domain peptide would also have the claimed activities. In addition, claims 1-3 and 11-13 are not limited to E domain peptide from Insulin-like growth factor 1, and it would require undue experimentation to identify other E domain peptide agents or homologs, and it would not be predictable that such an E peptide domain would inhibit proliferation and reduce the invasiveness of malignant cells. Therefore, the claims are not enabled for any other E domain peptide except for the Ea-2 and Ea-4 domain peptides of rainbow trout having the amino acid sequences of SEQ ID NOS: 2 and 4.

Due to the lack of direction/guidance presented in the specification regarding the absence of working examples directed to any other E-domain peptide, the complex nature of the invention, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8.1 Claims 21-23 are vague and indefinite because claims 21-23 recite "E domain peptide", and it is not clear what an E domain peptide is or where it is derived from. The independent claims should specify "E domain peptide **from Insulin Growth Factor-Like 1**" for clarity.

8.2 The claims are also indefinite because the, word "agent" makes it unclear how an E domain peptide agent differs from an E domain peptide.

Conclusion

9. No claim is allowed.

The art considered pertinent to the present application is Siegfried et al., PNAS, 89:8107-8111, Sept. 1992, which teaches that a human E peptide domain of insulin growth factor I has growth promoting effects on both normal and malignant bronchial epithelial cells. This reference does not teach or suggest what is being claimed, but is cited as the closest prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nichol can be reached at (571) 272-0835.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

Eileen B. O'Hara

EILEEN B. O'HARA
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